

**IMPROVED CONTAINERS FOR PHARMACEUTICALS,  
PARTICULARLY FOR USE IN RADIOISOTOPE GENERATORS**

**TECHNICAL FIELD OF THE INVENTION**

The invention is directed to improved containers for pharmaceuticals and the tubing and tubing connectors associated therewith, particularly containers for pharmaceuticals which are heated, irradiated or otherwise subjected to increased pressure. In a preferred embodiment, the invention is directed to an improved container for use in a radioisotope generator. Specifically, the designs and materials of the column container and its closure and associated tubing and tubing connectors have been improved.

## SUMMARY OF THE INVENTION

The invention includes improved pharmaceutical containers, particularly improved containers for pharmaceuticals that are subjected to increased pressure (such as by heating or other means) and/or are subjected to radioactivity. In a preferred embodiment, the invention is directed to an improved container, also called a column, for use in a radioisotope generator. In an especially preferred embodiment, the improved column is for use with rubidium-82 generator such as those disclosed in U.S. Patent Nos. 3,953,567; 4,400,358; 4,406,877; 4,562,829; 4,585,009; 4,585,941; and 5,497,951, incorporated herein by reference in their entirety. In a particularly preferred embodiment, the improved column is used in a rubidium-82 generator such as that sold under the trade name CardioGen®.

The improved pharmaceutical container of the invention includes an improved seal and crimping process, as well as changes to the design of the stopper and the container to prevent blockages and improve consistency in packing and closing the container, which improves flow rate and elution from the column.

Further improvements include constructing the container and stopper out of radiation resistant or tolerant materials. In addition, flexible tubing used with the container is made of a radiation resistant or tolerant material, and the Luer locks used to fasten the flexible tubing to the container is made of a radiation resistant or tolerant material and is further improved to insure a tight, secure lock which will not inadvertently loosen or disconnect.

Specifically, the improved container has a new, stronger seal which is used to crimp the stopper in a pharmaceutical container and particularly, which is used to seal a radioisotope generator column/stopper assembly system, such as the CardioGen® system. This improved seal prevents leakage, even at increased pressure, and reduces ballooning of the rubber stopper material. The seal has a configuration similar to one of those shown in Fig. 5B through Fig. 5F and Fig. 6 and is made of any suitably strong material including

metal or plastic. A pneumatically operated automatic or semi-automatic crimper, set at optimized pressure, is preferably used to crimp the seal during assembly of a pharmaceutical container such as a radioisotope generator column/stopper assembly system. The invention includes identification of optimized crimping pressure(s) for crimping the seal (regardless of material) to a pharmaceutical container such as a glass or plastic vial or column and thus securing in place a rubber closure(s) when using an automatic crimping system and/or manual crimping.

The stopper which is crimped into place is also improved. Specifically, it is made of a material which is radiation resistant or tolerant, is resistant to ballooning and can withstand at least the pressures at which the container operates. Additionally, the configuration and placement of the stopper are improved. For example, the improved stoppers form tight seals with the column and reduce the "dead volume" at the bottom of the column— space where non-radioactive, decayed eluate could mix with (and dilute) fresh, radioactive eluate, reducing the efficacy of the eluent.

The improved pharmaceutical container also includes improvements to the design which improve its packing/assembly and thus ensure specified flow of eluent through the container.

These improvements are illustrated in the context of a radioisotope generator column container. Flow rate of the eluent through the column could be partially or completely blocked if the stopper blocks the outlet arm of the column. As shown in Figure 1, the outlet arm of the container of the invention has been repositioned slightly and a small piece of plastic removed from the inside edge of the column to create a recess or notch where the outlet arm enters the column lumen to prevent a stopper from blocking flow. See Figure 4. A small reinforcement piece of resin is added to the outside of the column between the outlet arm and column body to provide additional strength.

Another improvement in the containers of the invention addresses consistency of assembly and packing of the containers. In prior columns for a radioisotope generator, a plastic basket or spacer was supplied separately and was placed on the top of the column packing before the seal was inserted and the seal crimped into place. In these prior columns, placement of the baskets or spacers, which hold the column packing in place, could vary significantly, potentially creating some problems with consistency in packing. In the improved columns, two small orientation knobs have been added to the outside of the top basket/spacer and the orientation knobs are positioned 180° apart. These knobs fit into two small slots cut into the wall of the column. This combination eliminates the potential variability of manual alignment and depth placement of the basket/spacer into the column and ensures a consistent fit every time. Critical to the function of the column is the alignment of the basket/spacer openings with the column inlet in the top arm. This prevents potential misalignment and consequent restricted flow and possible back pressure and also ensures consistent and timely output of eluent to the patient.

Another improvement is to make the column assembly out of a radiation resistant or tolerant material, such as radiation resistant polypropylene. Likewise, the flexible tubing and Luer connector are made of radiation resistant or tolerant materials, such as radiation resistant polyvinylchloride. Furthermore, the Luer connector on the flexible tube and its counterpart Luer connector on the column assembly are configured to provide for a tight lock which will not leak and which will not loosen or inadvertently disconnect during use.

## THE TECHNICAL PROBLEM AND ITS SOLUTION

The invention was designed to solve a number of technical problems experienced with prior art pharmaceutical containers.

### 1. Leakage From the Stopper/Column Interface

Leakage from the flange (or other area) of the seal of prior pharmaceutical containers such as column/stopper assembly systems was found to occur when the system was exposed to increasing pressure.

The new seal, consisting of a stronger material crimped at optimized crimping pressure, prevents leakage at the flange seal area even at increasing pressure.

### 2. Ballooning

Ballooning and/or burst of rubber materials (both before and after irradiation) through the center hole of current aluminum seals has been observed when they are subject to repeated pulsations of pressure cycling. The seals of the invention, which are stronger and are crimped at optimized pressure, reduce the likelihood of this problem. However, in a preferred embodiment the seal used in the improved container of the invention has a center hole of reduced size. For example, a seal with the configuration of those in Fig. 5B, Fig. 5C, Fig. 5E or Fig. 6 may preferably be used. Due to the small center hole and strength of these seals, and crimping at optimized pressure, ballooning and/or burst of rubber materials is prevented. Consequently, pharmaceutical containers of the invention, and particularly column/stopper systems of the invention, can be exposed to much higher pressures during use of the system in the field.

In addition, the larger surface area of the crimp resulting from the reduction of the diameter of the center hole serves as additional support for the rubber closure and inhibits possible rupture as it is weakened over time due to the cumulative effect of exposure to radiation from the column or container content.

Also, the stopper is made of a radiation resistant or tolerant material. This also helps prevent ballooning and bursting.

### **3. Leakage Through Puncture Points**

Leakage through puncture points has been observed in prior art pharmaceutical containers. Such leakage may be eliminated in containers of the invention through a combination of the stronger seal material, preferably a smaller center hole, and crimping at optimized pressure.

### **4. Splitting of the Seal**

Splitting or tearing of current aluminum seals has been observed at pressures intended for use with a pharmaceutical container system (or pressures to which the system can potentially be exposed during intended usage in the field).

Due to the strength of the new seal material, no splitting or rupture of seal material is observed at pressures intended for use. For example, the seals on the columns of the invention do not split or rupture when used in, for example, a rubidium generator at intended pressures.

### **5. Inconsistent Manual Crimping Procedure**

The manual crimping procedure commonly used with many prior container systems, including radioisotope column systems, is not always consistent and thus may not result in reproducible crimping pressures. Over-pressuring can result in buckling and collapse of the skirt of the seal material, the closure and/or the container. Under-pressuring can result in a loose overseal. Use of the automatic or semi-automatic crimping procedure of the invention with compressed or pressurized air results in consistent/reproducible crimping pressures, and enables selection of optimized crimping pressures when crimping various seal materials.

### **6. Maintenance of Consistent Flow/Reduction of Back Pressure**

In some prior pharmaceutical columns, flow rate of the eluent through the column could be partially or completely blocked because the stopper blocked the outlet arm of the column. The outlet arm of the container of the invention has been repositioned slightly and a small piece of plastic removed from the inside edge of the column to create a recess or notch where the outlet arm enters the column lumen to prevent a stopper from blocking flow. A small reinforcement piece of resin is added to the outside of the column between the outlet arm and column body to provide additional strength. The recessed outlet arm and notch near the bottom of the column body greatly reduces the chance of back pressure due to a stopper blocking the outlet arm.

#### **7. Inconsistent Positioning Within Column**

In a column for a radioisotope generator, a plastic basket or spacer is supplied separately and is placed on the top of the packed column before the seal or closure is inserted and the seal crimped into place. In prior columns, the baskets/spacers, which hold the column packing in place, were not easily positioned consistently both in terms of depth and orientation. In the improved columns of the invention, two small orientation knobs have been added to the outside of the top basket/spacer and these orientation knobs are positioned 180° apart. These knobs fit into two small slots cut into the wall of the column. This combination eliminates the potential variability of manual placement of the basket into the column, ensuring a consistent fit from generator to generator and reducing the variability in packing density associated with this manual process.

#### **8. Degradation Due To Radiation**

Many materials degrade when exposed to radiation. Degradation includes possible changes in color, loss of flexibility, increased brittleness and the leaching out of various substances from the materials. To avoid these potential problems, the column assembly,

stopper, flexible tubing and Luer connectors are made out of radiation resistant or tolerant materials.

Frequently, when a material is said to be radiation resistant or tolerant, that means the material can withstand the amount of radiation used for sterilization, which is typically about 25 kGy. For the purposes of the present invention, however, a material is radiation resistant or tolerant when it can be exposed to about 145 kGy radiation and not degrade to the point where the functioning of the column assembly will be adversely affected.

## **9. Properly Closed Luer Locks**

Luer locks are known in the art. However, it can be difficult to determine when a Luer lock has been sufficiently tightened to form a tight, non-leaking lock. Thus, one improvement is to provide for one or more tabs on each Luer connector. When the tabs achieve a certain orientation with respect to each other, for example when the tabs line up, such orientation means that the Luer lock has been sufficiently tightened.

Another potential difficulty with Luer locks is that they can come loose, i.e. disconnect, during use, which has the potential of causing a leak. To overcome this potential difficulty, the Luer connectors screw together and are each provided with one or more tabs. As the Luer connectors approach their fully tightened position, the tabs overlap. Further tightening causes the overlapping tabs to pass by each other, which can cause a clicking sound or sensation. When this occurs, the Luer lock is sufficiently tightened. Also, the Luer locks cannot become loose, e.g. unscrew, because the overlapping tabs will inhibit this action.



## BRIEF DESCRIPTION OF THE FIGURES

Figs. 1A through 1G illustrate the inventive column assembly from different angles and cross sections.

Figs. 2A through 2D illustrate an alternative embodiment of the inventive assembly from different angles and cross sections.

Figs. 3A through 3D illustrate a spacer or basket used in the inventive column assembly.

Fig. 4 illustrates a detailed view of the bottom of the inventive column assembly.

Fig. 5A is a prior art crimp seal.

Figs. 5B through 5F illustrate various crimp seals that may be used with the inventive column assembly.

Figs. 6A and 6B illustrate a preferred crimp seal.

Figs. 7A through 7D illustrate a stopper for use with the inventive column assembly.

Figs. 8A through 8D illustrate an improved Luer lock.

## DETAILED DESCRIPTION OF THE INVENTION

Referring now to Fig. 1, Fig. 1A shows a side view and Fig. 1B shows a bottom view of the inventive container (e.g., column assembly) of one embodiment of the invention. Fig. 1C is another side view of the inventive column assembly, cut along line A-A of Fig. 1B. Fig. 1D is detail B from Fig. 1C, at a scale of 3:1 compared to Fig. 1C. Fig. 1E is a top view of the inventive column assembly, cut along line E-E of Fig. 1A. Fig. 1F is another side view of the inventive column assembly, cut along line C-C of Fig. 1B. Fig. 1G is detail D of Fig. 1F, at a scale of 2:1 compared to Fig. 1F.

Fig. 1A has an inlet arm 1 which has an inlet arm female Luer cap 2 at its distal end. The proximal end of the inlet arm 1 attaches to the upper portion of a column 3. There is also an inlet arm support means 4 to support the inlet arm 1. The support means is preferably material which is added to support the inlet arm 1. Preferably, this material is the same material used to construct the column assembly. As shown, the inlet arm support means 4 is a triangular shaped member attached to the inlet arm 1 and the column 3, although the shape of the support is not limited to a triangle. It can be square, a bar passing from the inlet arm 1 to the column 3, or any other suitable shape.

The column 3 has a top portion 5 and a bottom portion 6. The top portion 5 comprises a first top portion 7 and a second top portion 8. The first top portion 7 is on top of and has a diameter greater than the second top portion 8, which is on top of and has a greater diameter than the column 3.

The bottom portion 6 of the column 3 has a similar configuration. It has a first bottom portion 9 and a second bottom portion 10. The first bottom portion 9 sits below and has a greater diameter than the second bottom portion 10, which sits below and has a greater diameter than the column 3. Also shown is a bottom stopper 11.

An outlet arm 12 is attached to the bottom portion of the column 3. The distal end of the outlet arm 12 terminates in an outlet arm female Luer cap 13. There is also an outlet arm support means 14 to support the outlet arm 12. The support means is preferably material which is added to support the outlet arm 12. Preferably, this material is the same material used to construct the column assembly. As shown, the outlet arm support means 14 is a triangular shaped member which attaches to the column and the outlet arm 12, although the shape of the support is not limited to a triangle. It can be a square, a bar passing from the outlet arm 12 to the column 3, or any other suitable shape.

Fig. 1C shows a cross section of the inventive column assembly, cut through line A-A of Fig. 1B. As shown, the inlet arm 1, column 3 and outlet arm 12 are hollow.

Turning to the hollow interior or lumen of the column 3, it first defines a top stopper receptacle area 15. Below that and in communication with it is a top basket receptacle area 16. As shown in Fig. 1C, the top basket receptacle area 16 contains a top basket or spacer 17. Following that is a packing material containing area 18. Underneath the packing material containing area 18 is a bottom screen 19, followed by a bottom open area 20. Underneath the bottom open area 20 is a bottom stopper receptacle area 21.

Fig. 1C shows the bottom stopper 11 inserted into the bottom stopper receptacle area 21 of the column 3. Note that the bottom stopper 11 consumes most of the bottom stopper receptacle area 21. This minimizes the dead volume in the bottom stopper receptacle area 21. Minimization of the dead volume minimizes mixing of fresh, radioactive eluent with non-radioactive or decayed eluent, which could dilute the fresh eluent, thereby maintaining a narrow rubidium-82 bolus profile.

The inlet arm 1 and outlet arm 12 are each hollow, the hollow portions being 22 and 23 respectively, and are in communication with the hollow portion of the column 3. As

shown in Fig. 1C, the hollow portion 22 of the inlet arm 1 is in communication with the top basket receptacle area 16.

The intersection of the column 3 and the outflow arm 12 is shown in more detail in Fig. 1D. As shown therein, no portion of the outflow arm 12 extends into the hollow portion of the column 3, as was the case with certain prior art column assemblies. Also, the hollow portion 23 of the outflow arm 12 intersects the hollow portion of column 3 at the top of the bottom stopper receptacle area 21 or at about the place the bottom stopper receptacle area 21 and the bottom open area 20 intersect. This configuration, not found in prior art column assemblies, prevents the bottom stopper 11 from blocking the outflow arm 12.

In a preferred embodiment, an outflow notch 25 is formed where the hollow portion 23 of the outflow arm 12 intersects the hollow interior of the column 3, thus further preventing any blockage of the outflow arm 12 by the bottom stopper 11. This embodiment is shown in more detail in Fig. 4.

Fig. 1E is a top view of the inventive column assembly. Visible from this perspective are, for example, the top basket or spacer 17 and the top basket receptacle area 16. Also shown are notches 24a and 24b.

The notches 24a and 24b are made in the wall of the top basket receptacle area 16. As shown in Fig. 1E, they are 180 degrees opposed to each other. They are configured to cooperate with a pair of protrusions which appear on a top basket (discussed below with respect to Fig. 3) such that the protrusions fit into notches 24a and 24b. This configuration insures proper placement of the top basket into the top basket receptacle area 16 so that the top basket is straight and at the correct depth. In prior art column assemblies, which lacked these notches and protrusions, it was possible to insert the top basket in such a manner that it was not straight and/or at the wrong depth, which adversely affected the function of the column assembly.

Fig. 1E shows two notches **24a** and **24b** 180° opposed to each other. It is understood that the present invention is not limited to this configuration. Rather, there can be 1, 3, 4, 5, 6 or more notches or even a ledge present in the wall of the top basket receptacle area **16** in any configuration, so long as these notches (or ledge) cooperate with protrusions on the top basket to insure its proper fit.

Fig. 1F shows a side view of the inventive column assembly, cut along line C-C of Fig. 1B. Fig. 1G is detail D of Fig. 1E, showing an alternative embodiment for the first top portion **7a**. As shown in Fig. 1G, this first top portion **7a** slopes downwardly from its top, whereas the first top portion **7** of Fig. 1F is squared off, i.e., non-sloping.

Fig. 2 shows an alternative embodiment of the inventive column assembly. As shown in Fig. 2D, which is detail B from Fig. 2C at a scale of 3:1, the bottom stopper **11a** is configured to fit into substantially all of the space of the bottom stopper receptacle area **21**. This insures a better fit between the outer wall of the bottom stopper **11a** and the inner wall of the bottom stopper receptacle area **21**, thus further insuring against any leaks. In addition, the stopper **11a** reduces the dead volume in the bottom stopper receptacle area **21**. Minimization of the dead volume minimizes mixing with non-radioactive or decayed eluent, which could dilute the fresh eluent, thereby maintaining a narrow rubidium-82 bolus profile. The bottom stopper **11a** further comprises a bottom stopper hollow space **11b**. This bottom stopper hollow space **11b** helps prevent the bottom stopper **11a** from blocking the outflow arm **12**.

The column assembly is preferably made of polypropylene. Prior art column assemblies were made with H5820 polypropylene. While that product can still be used, in a preferred embodiment the polypropylene random copolymers PP P5M4R-034 or PP 13R9A (Huntsman Polymers (The Woodlands, TX)) can be used because they are more resistant to radiation than the prior art H5820 polypropylene. See the Prospector X5 data sheets with

ATSM and ISO properties for PP P5M4R-034 and PP 13R9A, which are incorporated herein by reference in their entirety. Of the two Huntsman polypropylenes, PP 13R9A is the more preferred, based upon UV profile, Instron stress testing and appearance after gamma-irradiation.

The manufacturing process for the inventive column assembly has also been improved. A new automatic mold has been designed which improves the quality and appearance of the column assembly, and which increases the efficiency of the manufacturing process. Manufacturing is presently done by Duerr Molding (Union, N.J.).

For example, pins are used to form the hollow portions of the inlet arm **22** and outflow arm **23**. In the prior art molding process, these pins were not fixed, so they floated. As a result, the side wall thickness of the inlet arm **1** and outlet arm **12** varied. In the present process, the pins are fixed. Therefore, the thickness of the side walls is more uniform.

Also, as described above, the position of the outflow arm **12** has been moved, the outflow arm no longer protrudes into the hollow interior or lumen of the column **3**, and the outflow arm resides in a recess or notch. This prevents the outflow arm from being blocked. Furthermore, support means **4**, **14** are provided to strengthen the inlet arm **1** and the outflow arm **12**. In addition, notches **24a** and **24b** are provided for the proper placement of the top basket.

Further improvement to the manufacturing process and column assembly are described throughout the instant specification.

The packing material area **18** of the column **3** is designed to receive packing material. The type of packing material used depends upon the intended use of the column arrangement.

When used as, for example, a rubidium-82 generator, such as CardioGen®, the packing material is one which will adhere strontium-82 but will allow for the elution of rubidium-82. Strontium(II)-82 decays into rubidium(I)-82. Elution of strontium-82 is not

desired because it binds to bone and exposes the patient to unnecessary radiation exposure. Presently, stannic oxide is the preferred packing material.

The packing material is loaded into the column **3** in a conventional manner. The column **3** is then loaded with strontium-82 in a conventional manner. For example, the closure is punctured by a needle (or similar device) containing the strontium-82 solution. The strontium-82 solution is slowly added to the top of the packed column and allowed to flow through it by the force of gravity. If necessary, a small vacuum can be used. Also, the packing material is preferably wetted before the strontium-82 is added. Slow addition of the strontium-82 is preferred because it will result in the strontium-82 being absorbed as close to the top of the column as possible.

Filters, preferably fiberglass filters, can also be used in this conventional loading procedure. For example, two fiberglass filters are first placed in the column **3**, then a portion of the packing material is added, followed by a single fiberglass filter, then the remainder of the packing material, then two more fiberglass filters. Once filled, the top basket or spacer **17** is inserted into the top basket receptacle area **16**. The top basket **17** acts as a retainer to hold the packing material in place.

Fig. **3** shows schematics of the spacer or top basket **26** of the inventive column assembly. The spacer or top basket **26** is cylindrical in shape with an open top portion **27** and a screen **28** at the bottom portion **29**. Another top basket or spacer **17** of similar configuration is shown in Fig. **1**, placed in the top basket receptacle area **16**.

As shown in the embodiment of Figs. **3B** and **3D**, the top basket **26** actually has three cylindrical areas, a top cylindrical area **30**, a middle cylindrical area **31** and a lower cylindrical area **32**. The top **30** and bottom **32** cylindrical areas have diameters about equal to each other, and their diameters are greater than the diameter of the middle cylindrical area **31**.

The top basket **26** also contains protrusions **33a**, **33b** which are designed to cooperate with notches **24a**, **24b** in the top basket receptacle area **16**. In operation, the protrusions **33a**, **33b** fit into the notches **24a**, **24b** to insure proper alignment of the top basket **26** in the top basket receptacle area **16**. When so positioned, the top basket **26** acts as a retainer to hold the packing material in place.

As shown in Figs. **3A** and **3C**, the two protrusions **33a**, **33b** are 180° opposed to each other. They are located at the top cylindrical area **30**. As was the case with the notches **24a**, **24b**, the present invention is not limited to this configuration. Rather, there can be 1, 3, 4, 5, 6 or more protrusions, in any orientation, so long as they cooperate with the notches to help insure a proper fit for the top basket **26**.

The top basket **26** also contains a side opening **34**. As shown in Figs. **3B** and **3D**, the side opening is in the middle cylindrical area **31** of the top basket **26**. The purpose of the side opening is to line up with the inlet arm **1** when the top basket **26** is placed in the top basket receptacle area **16**. In this arrangement, when a liquid is introduced into the inlet arm **1**, it will pass through the side opening **34** into the top basket **26**.

The top basket **26** can be made of any suitable material, such as polypropylene. Preferably, the material will be radiation resistant, i.e. resistant to degradation in the presence of a radioactive material. More preferably, the top basket **26** is made of the same material used to construct the column assembly. In a preferred embodiment, that material is PP P5M4-R-034 or PP 13R9A polypropylene (Huntsman Polymers (The Woodlands, TX)). Even more preferably, the material is the PP 13R9A polypropylene. In a yet further preferred embodiment, the top basket **26** is molded at the same time the rest of the column assembly is molded.

As discussed above, Fig. **4** shows a detailed view of the bottom **6** portion of the column **3**. Fig. **4** shows the outflow notch **25** where the hollow portion **23** of the outflow arm



12 intersects the hollow interior of the column 3. The outlet notch 25 prevents blockage of the hollow portion 23 of the outflow arm 12 by the bottom stopper 11 (not shown in Fig. 4).

Fig. 5 shows various types of crimp seals to use with the present invention. Fig. 5A shows the current, prior art crimp seal. Figs 5B-5F show various alternate embodiments of the crimp seal.

The function of the crimp seal is to form a tight, crimped seal between the stoppers (described below) and the pharmaceutical container to prevent leakage. Also, a central hole is provided in the crimp seal to allow for the insertion of a needle or similar device. In one preferred embodiment the pharmaceutical container is a column, or column assembly, such as one used in a rubidium generator.

The crimp seal can be made of any material, such as plastic or metal. The material should preferably be radiation resistant, and of sufficient strength to withstand pressures of at least 90 psi and preferably up to 160 psi. More preferably, the material should be metal. Preferred metals comprise aluminum, steel and tin, or suitable alloys or mixtures thereof. The metal can be optionally coated. For example, tin coated steel can be used.

The diameter of the crimp seal will vary according to use, for example, vary according to the diameter of the pharmaceutical container which is to be crimped. With respect to a column assembly to be used as a rubidium-82 generator, such as CardioGen®, the diameter of the crimp seal is preferably about 20 mm across its top.

Fig. 5A shows a conventional prior art crimp seal 35. It is made out of aluminum which is about 0.2 mm thick, has a flat top portion 36 with a diameter of about 20 mm with central hole 37 of about 9.5mm in diameter and a skirt 38 about 7.5mm high.

There are several potential problems with this prior art crimp seal. First, because aluminum with a thickness of only about 0.2 mm is used, the crimp seal might not be strong enough to insure a strong, leakproof seal. Second, the central hole 37 is large, and therefore

the stopper might not be properly supported. Also, the larger central hole 37 may allow for ballooning of the stopper. Third, this crimp seal is manually crimped to the column 3. Manual crimping can result in undesirable variability of crimping pressure and, accordingly, can affect how well the crimp seal 35 seals the column 3 to prevent leakage.

Fig. 5B shows one type of useful crimp seal 39. This crimp seal 39 comprises two parts, a top crimp member 40 and a bottom washer 41. Both the top crimp member 40 and the bottom washer 41 are made of aluminum (vendor –West). The thickness of the aluminum for each part can vary depending upon the intended use, but the aluminum used for each member is generally about 0.2 mm thick.

The top crimp member 40 has a central hole 42 and a skirt 43. The size of each, and the diameter of the crimp seal, can vary depending upon use. As shown in Fig. 5B, the central hole 42 has a diameter of about 6.4mm and the skirt 43 is about 7.6mm high. The diameter of the top crimp member 40 is about 20 mm. The top crimp member 40 also has a cover 44, which covers the central hole 42 when not in use but can be pulled or peeled back when in use. Also, while none of Figs. 5C through 5F or Fig. 6 show a cover, it is understood that each of these embodiments can employ a cover if desired.

Fig. 5B also employs a bottom washer 41. The bottom washer 41 contains a central hole 45. The bottom washer central hole 45 can have a diameter greater than, the same as or smaller than the diameter of the central hole 42 in the top crimp member 40. As shown in Fig. 5B, both central holes 45, 42 have about the same diameter, i.e. about 6.4mm. The bottom washer 41 does not have a skirt. The diameter of the bottom washer 41 is about 20 mm.

When used, the bottom washer 41 is placed below the top crimp member 40 and both are crimped into place. Crimping is preferably performed via an automatic or semi-automatic

crimper, which is discussed in more detail below. In the alternative, other processes which control the crimping pressure applied can be used.

Fig. **5C** shows another embodiment of the inventive crimp seals. This crimp seal **46** comprises a single member. It is made out of steel (vendor – Microliter). The thickness of the steel can vary according to the intended use, but is generally about 0.2 mm thick. This crimp seal **46** is about 20 mm in diameter, contains a central hole **47** of about 5.0mm in diameter and has a skirt **48** about 7.2mm high. The crimp seal **46** is preferably crimped into place using an automatic or semi-automatic crimper, although other processes which control the pressure applied can be used.

Fig **5D** shows yet another embodiment of the inventive crimp seals. This crimp seal **49** comprises a single member. It is made out of steel (vendor – Microliter). The thickness of the steel can vary according to the intended use, but is generally about 0.2 mm thick. This crimp seal **49** has a diameter of about 20mm, contains a central hole **50** of about 8.0mm in diameter and a skirt **51** about 7.2mm high. The crimp seal **49** is preferably crimped into place using an automatic crimper, although other processes which control the pressure applied can be used.

Fig. **5E** is yet still another embodiment of the inventive crimp seals. This embodiment comprises two parts, a top crimp member **52** and a bottom washer **53**. Both the top crimp member **52** and the bottom washer **53** are made of aluminum (vendor – Microliter). The thickness of the aluminum can vary depending upon the intended use, but the aluminum used for each member is generally about 0.2 mm thick.

The top crimp member **52** has a central hole **54** and a skirt **55**. The central hole **54** has a diameter of about 9.6 mm and the skirt **55** is about 7.6 mm high. The top crimp member **52** has a diameter of about 20mm.

The top crimp member **52** also contains an insert **56**, which is seated in or under the central hole **54**. The insert **56** can be made of any suitable substance, but is preferable made of metal, such as steel, aluminum or tin, or plastic. The insert **56** also contains an insert central hole **57**, which has a diameter of about 5 mm.

The bottom washer **53** also has a central hole **58**, which has a diameter of about 5 mm. The bottom washer **53** is about 20 mm in diameter and it does not have a skirt.

When used, the bottom washer **53** is placed below the top crimp member **52** and the insert **56** and then all are crimped into place. Crimping is preferably performed using an automatic or semi-automatic crimper, although other processes which control the pressure applied can be used.

Fig. **5F** shows yet another embodiment of the inventive crimp seals. Like Fig. **5E**, Fig. **5F** employs two members, a top crimp member **59** and a bottom washer **60**. Both members are made of aluminum (vendor-Microliter). While the thickness of the aluminum can vary with the intended use, generally each member is about 0.2 mm thick.

The top crimp member **59** contains a central hole **61** and a skirt **62**. The central hole **61** has a diameter of about 9.6 mm and the skirt **62** is about 7.6 mm high. The top crimp member **59** has a diameter of about 20mm.

The bottom washer **60** also has a central hole **63**. The bottom washer central hole **63** has a diameter of about 11.4 mm. The diameter of the entire bottom washer **60** is about 20mm. The bottom washer **60** does not have a skirt.

When used, the bottom washer **60** is placed below the top crimp member **59**. Both are then crimped into place. Preferably, an automatic crimper is employed, although other processes which control the pressure applied can be used.

Fig. **6** is an alternate and preferred embodiment of the inventive crimp seals. This crimp seal **64** comprises a single member. It is made out of steel (vendor – Microliter), code

#20-000 M. See the Microliter Product Catalog, which is incorporated herein by reference in its entirety. The thickness of the steel is about 0.20 mm.

The crimp seal 64 contains a central hole 65 and a skirt 66. The central hole 65 is about 5.00 mm  $\pm$  0.25 mm in diameter and the skirt 66 is about 7.00 mm  $\pm$  0.25 mm high. The entire crimp seal 64 has a diameter of about 20.75 mm  $\pm$  0.25 mm. The crimp seal 64 is preferably crimped into place using an automatic or semi-automatic crimper.

Fig. 7 shows an improved stopper 67 to be used with the inventive column assembly. The stopper 67 is preferably made from a material which will form a tight seal with the column assembly. In a preferred embodiment the stopper 67 is made of a material which is also resistant to radiation.

Prior art stoppers were made of materials such as Itran-Tompkins PT-29 green neoprene rubber. This material had two potential disadvantages. First, it could degrade when exposed to radiation. Second, it contained latex, which could cause allergic reactions.

Various materials were compared to the PT-29 green neoprene used in the prior art. These materials included neoprene, isoprene, bromobutyl, chlorobutyl, nitrile, isoprene/chlorobutyl, EPDM (ethylene propylene diene monomer) and Viton®. These materials were coated, uncoated, siliconized and non-siliconized.

These materials were made into column assembly stoppers and were irradiated simulating the exposure from a 100mCi generator over a time period of 45 days (about 145 kGy). Irradiated stoppers were compared to non-irradiated controls by integrity (pressure) testing of the column/stopper assemblies. Assemblies were pressurized to determine load pressure required to cause ballooning of rubber materials or leaks/burst at the seal closure (up to about 200 psi). In addition, for the purpose of determining potential rubber extractables and/or leechables, additional column/stopper assemblies were irradiated in the presence of

0.9% saline solution. The saline solution was then scanned at 250mm for UV absorbing extractables.

Three elastomeric compositions were identified as suitable to use in the stoppers of the invention: West Pharmaceutical Services (Lionville, PA) 4588/40 isoprene/chlorobutyl; American Stelmi (Princeton, NJ) 6720 bromobutyl; and Helvoet-Pharma (Pennsauken, NJ) Helvoet FM 140/0 chlorobutyl. Of these materials, the most preferred product to use is the West 4588/40 isoprene/chlorobutyl. Other materials may be used as long as they provide the stopper characteristics specified herein.

The stopper 67 should be configured so that it forms a tight seal with the column assembly and minimizes the dead volume (mixing), thus maintaining a narrow rubidium-82 bolus profile and maximizing efficiency. One preferred structure for the stopper is shown in Fig 7.

Referring to Fig 7B, the stopper 67 comprises a generally cylindrical top section 68 and a generally cylindrical bottom section 69. The diameter of the stopper bottom section 69 is about the same as or slightly larger than the inside diameter of the first top portion 7 and first bottom portion 9 of the cylinder 3, assuming both of these portions 7, 9 have the same diameter. If these portions have different diameters, then the cylindrical bottom section 69 of the stopper 67 will have about the same or slightly larger inside diameter as the portion 7, 9 it is intended to be inserted into. The reason for this configuration is to insure a tight fit between the stopper 67 and the first top 7 and first bottom 9 portions of the cylinder 3. A tight cylinder 3/ stopper 67 interface helps prevent leakage.

The stopper top section 68 has a greater diameter than the stopper bottom section 69 to prevent the stopper 67 from being inserted too far into the cylinder 3. In addition, optionally the stopper top section 68 can have a curved upper edge 70.

The stopper bottom section **69**, in one preferred embodiment, contains a U-shaped groove **71** in its base. See Fig 7A. The U-shaped groove **71** traverses greater than half the length of the stopper bottom section **69**, and it terminates in a semi-circular section **72**. Preferably, the center point **73** of the semicircular section **72** should be about at the center point of the stopper bottom section **69**.

The stopper top section **68** contains a central circular indentation **74** in its top surface. See Fig 7C. Preferably, the diameter of the central circular indentation **74** has a diameter about equal to the width of the U-shape groove **71**. As shown in Figs **7B** and **7D**, the central circular indentation **74** and the U-shaped groove **71** should preferably line up with each other when the stopper is viewed through its cross-section. The central circular indentation **74** and U-shaped groove **71** allow for easy insertion of a needle or similar device into the stopper **67**.

The surface of the stopper top section **68** also contains three spherical dots **75a**, **75b**, **75c** and an indicia, such as a spherical lug **76**. They are spaced equidistant from each other around the central circular indentation **74**. Also, the spherical lug **76** is placed so that it is above the U-shaped groove **71**. In this configuration, when the stopper **67** is inserted into the first top portion **7** of the column **3**, the spherical lug **76** can be lined up with the inlet arm **1**. Thus, the open end of the U-shaped groove **71** will face the inlet arm **1**, thus preventing its blockage.

The same holds true for the first bottom portion **9** of the column **3**. When the stopper **67** (stopper **11** shown in Fig. **1** and stopper **11b** in Fig. **2** can have the same or different configurations from stopper **67**) is inserted therein, the spherical lug **76** is lined up with the outlet arm **12**. The open end of the U-shaped groove **71** will then face the outlet arm **12** and prevent its blockage.

It is understood that the present invention is not limited to a U-shaped groove **71**. Any other configuration, such as a notch, can be used so long as any potential blockage is

avoided. In fact, if there is no potential for blockage, the U-shaped groove 71 or alternative structure can be eliminated.

The stopper 67 is affixed to the column 3 via crimping, using the crimping seals described above in Figs. 5 and 6. In the prior art, crimping was performed manually. The disadvantage of manual crimping is that it is not always uniform. One problem this can cause is leakage. To overcome this potential problem, the present invention preferably uses automatic or semi-automatic crimping.

Any automatic or semi-automatic crimper can be used for the present invention, so long as it can consistently crimp seals at a specified, controlled pressure. One preferred type of automatic crimper is a pneumatic crimper, which is powered by gas. One example of a pneumatic crimper suitable for the present invention is an AP/CP2000 Lightweight Air Crimper/Decapper (Laboratory Precision Limited, UK). See Laboratory Precision Limited brochure copyrighted April 4, 2001, which is incorporated herein by reference in its entirety.

In the crimping process, a stopper 67 is inserted into the top portion 5 or bottom portion 6 of the column 3, so that it is seated in the first top portion 7 or first bottom portion 9, respectively. A crimp seal or a crimp seal and washer (see Figs. 5 and 6) is/are placed over the stopper 67. The crimp seal or crimp seal and washer are then crimped into place, either manually or, preferably, automatically or semi-automatically. While the crimping pressure used is optimized based upon the configuration and material of the crimp seal and stopper, generally about  $117 \pm 3$  psi pressure is used.

The resulting crimped crimp seal/stopper configuration can withstand the operative pressures of the system and can further withstand pressures of at least 90 psi and preferably up to 200 psi.

When in operation, connector tubes (not shown) are connected to the column assembly. Referring to Fig 1A, both the inlet arm 1 and the outlet arm 12 have a female Luer



cap 2, 13 at their distal ends. These female Luer caps 2, 13 engage male Luer caps at the proximal ends of the connector tubes.

Prior art connector tubes can discolor from clear to brown and harden upon prolonged exposure to radiation. Also, the Luer connector can discolor and become brittle. In addition, the Luer connectors can loosen or become unintentionally disconnected during shipping or use.

Accordingly, the present invention includes constructing connector tubing out of radiation resistant materials. Preferably, the tubing is made from a flexible radiation resistant polyvinyl chloride (PVC) and the Luer connector is made from a rigid radiation resistant PVC. For example, a preferred material for constructing the tubing is AlphaGary PVC 2232 A/R-78S Clear 030X. See AlphaGary Test Result Certificate, Report Date 8/20/99; Technical Data, Date of Origin 8/99; and Material Safety Data Sheet printed 04/05/00; which are incorporated herein by reference in their entirety. A preferred material for constructing the Luer connector is AlphaGary PVC 2212 RHT/1-118 Clear 080X. See AlphaGary Data Sheet, Revision Date 4/02, which is incorporated herein by reference in its entirety. Also, using this AlphaGary rigid PVC for the Luer connector allows the heat bonding of tubing to the Luer connector.

The present invention further includes an improved Luer lock. The improvements are described below. An embodiment of this improved Luer lock is set forth in Fig. 8. These improved Luer locks can be used with the pharmaceutical containers of the present invention, or in any other indication where it is desirable to have a connection that will not inadvertently loosen or disconnect.

In the embodiment of Fig. 8, Fig 8A show a side view of the inventive column assembly with the inlet arm 1 projecting forward. Also shown is the female Luer cap 2 at the distal end of the inlet arm 1.

As shown in Fig. 8C, the female Luer cap 2 terminates in a flange 77. The flange 77 can be flat or, as shown, contain a groove 78. Other configurations, known in the art, can also be used.

The flange 77 is configured to engage and mate with threads 78 in a male Luer cap 79. When the two caps 2, 79 are screwed together, they form a tight Luer lock which will be leak resistant. This configuration is shown in Fig. 8D.

One difficulty with a Luer lock is to know when the male and female caps 79, 2 have been connected sufficiently to form a tight lock. To overcome this problem, one or more tabs are provided on each of the male 79 and female Luer caps 2. As shown for example in Figs. 8C and 8D, two tabs are provided on each cap 80a, 80b, 81a and 81b, although it is understood that the invention is not limited to this configuration only. For example, each of the Luer caps can also contain 1, 3, 4, 5, 6 or more tabs.

In one embodiment, the female Luer cap tabs 80a, 80b and the male Luer cap tabs 81a, 81b are so positioned that when the Luer locks is sufficiently tight, the tabs line up with each other. This way, a user knows when tightening is completed. The present invention, however, is not limited to this one configuration, so long as the tab or tabs on each of the Luer connectors 79, 2 are arranged in a desired configuration to demonstrate that the Luer connectors 79, 2 are sufficiently tightened. In another preferred embodiment, as shown in Fig 8D, the male Luer cap tabs 81a, 81b overlap with the female Luer cap tabs 80a, 80b. The tabs are so positioned that this overlap occurs when the tightening is complete. At the point of desired tightening, the tabs 80a, 80b, 81a, 81b pass by or click past each other. That way, the Luer locks cannot be over- or under-tightened. Also, inadvertent loosening or disconnection of the Luer lock during use or shipping is prevented by the overlapping of the tabs, preventing the Luer connectors 79, 2 from turning in a loosening direction.

When the inventive column assembly is used as, for example, a rubidium-82 generator, it is pre-packaged with strontium-82 in the factory. That is, the product shipped to the customer is radioactive. Therefore, the radioactive column assembly is shipped in a shielded (e.g. lead) container.

Nevertheless, leakage is still a concern upon shipping. Thus, to improve safety when the radioactive column assembly is shipped, an inventive improvement is to ship the product with a liquid absorbent pad. Preferably, the shipping pad is a GP100 absorbent pad (Shell Packaging Corporation, Springfield, NJ). GP100 is a 100% polypropylene non-woven mat of randomly oriented micro-fibers (2-10 micron diameters). See SPC General Product Specifications for GP100 dated May 26, 2003, which is incorporated herein by reference in its entirety. This type of shipping pad, which may have various configurations, thicknesses or absorbent capacities, is useful in absorbing any leaks which may occur.

## SUMMARY OF THE PREFERRED EMBODIMENTS

### Improved Seal

The new seal, which is used to crimp the rubber stopper in place in a pharmaceutical container and particularly, which is used to seal a radioisotope generator column/stopper assembly system, such as CardioGen®, is preferably made of a sufficiently strong material to eliminate the problems discussed above. Figs. 5B through 5F and Fig. 6 illustrate various method of reinforcing the top portion of the seal by use of a second layer (washer) or use of a stronger material such as steel/tin in addition to reducing the size of the center hole. The material may include metal or plastic, but is preferably metal. The metal may include heavy gauge aluminum, steel or tin, but is preferably steel or tin. The seal generally has the configuration shown in Fig. 5B through 5F and Fig. 6 and may have a small or large central hole, a shorter or longer skirt and optionally, a cover (e.g., plastic or aluminum over the central hole). The dimensions of the seal will vary, and one skilled in the art will understand that they should be appropriate to the container which is being sealed. Approximate dimensions for seals for a radioisotope generator column are shown in the various examples, in Figure 5 and in Fig. 6. These dimensions are approximate and are not intended to be limiting.

The central hole of the seals of the invention may vary in size. In a preferred embodiment the seal has a smaller central hole such as, for example, those proportional to the central holes shown in Fig. 5B, Fig. 5C, Fig. 5E and Fig 6.

In one embodiment, seals of Fig. 5B through Fig 5F and Fig. 6 are used to seal a radioisotope generator column. These seals are available from the vendors West Pharmaceutical Services (Lionville, PA) and Microliter Analytical Supplies Inc. (Suwannee, GA). In a particularly preferred embodiment, the central hole of the seal is reduced in size such as in the seals in Fig. 5B, Fig. 5C, Fig. 5E and Fig. 6. The preferred configuration for

this application is a 1-piece steel/tin crimp with a center hole of approximately 4-5 mm diameter and a skirt length of approximately 7.2 to 7.5mm as shown in Fig. 6.

The combination of using a stronger material such as steel/tin or heavier gauge aluminum and reduction of the center hole results in optimum performance in maintaining a secure leakage free seal under high pressure and particularly repeated exposure (pulsing or cycling) to high pressure as occurs with the use of the rubidium-82 generator as the enlarged surface area of the crimp limits excessive expansion of the rubber closure under pressure.

The use of a stronger material such as steel/tin or heavy gauge aluminum further improves the performance of the crimp by reducing the likelihood of failure due to relaxation or fatigue of the seal flange which is formed at the point where the crimp skirt is folded under the column or container flange when exposed to high or pulsating pressures. It is understood that the skirt length can be varied to provide a proper fit with the container/rubber seal combination to which it is applied.

### **Improved Seal**

In a preferred embodiment improved stoppers are used. Such stoppers are made of a radiation resistant material, preferably isoprene/chlorobutyl and most preferably West 4588/40 isoprene/chlorobutyl. Additionally, the configuration and placement of the stoppers are improved so that they form tight seals with the column, do not block the inlet or outlet arms and reduce the "dead volume" at the bottom of the column. In a preferred embodiment the stoppers are designed to facilitate insertion of a needle or similar device and contain indicia indicating proper insertion orientation. In the most preferred embodiment, the stoppers have the configuration shown in Fig 7A, Fig 7B and Fig. 7C.

### **Automatic Crimper and Improved Crimping Process**

In a preferred embodiment, an automatic or semi-automatic crimper is used to crimp the seals of the invention. The automatic or semi-automatic crimper is set at an optimized

pressure and is able to crimp seals of any material during assembly of a pharmaceutical container such as a radioisotope generator column/stopper assembly system. Suitable automatic crimpers include pressurized and/or compressed air crimpers such as those available from Laboratory Precision Limited under the trade name/model number AP/CP2000. Use of the automatic or semi-automatic crimping procedure of the invention with compressed or pressurized air results in consistent/reproducible crimping pressures, and enables selection of optimized crimping pressures when crimping various seal materials.

Use of optimized pressures improves the performance of the seals of the invention and also improves performance of seals of only moderate strength, such as lighter gauge aluminum and some plastics.

The automatic or semi-automatic, pneumatically powered crimper used to apply the seal is preferably operated at an optimized pressure of between 60 – 140 psi. However, although automatic or semi-automatic crimpers are preferred, it should be noted that application of the seal is not limited to automated equipment, and systems ranging from manual to fully automatic may be used, provided their operation can be optimized to produce repeatable and consistent predetermined pressures in applying the seals.

#### **Column Design Improvements**

Manufacturing Process: To create the new column design, a new automatic mold has been designed. The mold and the new columns produced therein exhibit improved column quality and appearance. The new mold also increases the efficiency of the manufacturing process. The increased speed of the new automated mold enables one operator to run the process efficiently.

Column Design: The improved pharmaceutical container also includes improvements to the design which ensure specified flow of eluent through the container and improve its packing and consistency. In one embodiment the improved container comprises a column

used in a radioisotope generator. The improved column includes a repositioned outlet arm, and the column outlet resides in a recess or notch in the inside ledge of the column where the outlet arm enters the column lumen, to prevent a stopper from blocking the flow. These improvements further include introducing small reinforcement pieces of resin to the outside of the column between the outlet arm and column body and between the inlet arm and column body to provide additional strength. Additionally, the seam of the inlet and outlet arms has been eliminated by changing the mold runners. This change has improved the consistency of the inlet and outlet arm diameters and made the arms stronger.

Furthermore, to address consistency of packing of the containers, two small alignment slots have been cut into the wall of the column to receive the orientation knobs on the baskets that properly align and seat the basket in the column and limit the insertion depth into the column. This improves the consistency of packing density and eliminates potential blockage of the inlet arm. Additionally, in one embodiment, the improved column has stopper flanges and Luer flanges with much smoother surfaces with sharper edges to improve the sealing ability of the crimp. These attributes improve stopper and Luer contact to the column and greatly reduce the chance of leakage. Also, the flashing on the column is reduced greatly to enhance the appearance of the part.

Finally, the column assembly is made from a radiation resistant or tolerant material. The most preferred material is Huntsman PP 13R9A polypropylene.

#### **Luer Lock and Connector Tube Improvements**

The Luer locks and connector tubes used with the column have also been improved. First, the connector tubes are made from a radiation resistant or tolerant material. Preferably, this material is AlphaGary PVC 2232 A/R-78S clear 030X.

Second, the terminal end of the connector tube which attaches to the column contains a male Luer cap. This male Luer cap is made of a radiation resistant material, preferably AlphaGary PVC 2212RHT/1-118 clear 080X.

Third, the male and female Luer caps screw together and each contains tabs, preferably two tabs each. When the tabs line up with each other in one embodiment or overlap with each other in another embodiment, that indicates that the two Luer caps are sufficiently tightened or screwed together to form a tight seal or lock. Also, in a preferred embodiment the overlapping tabs prevent the Luer caps from becoming loose, ie unscrewing inadvertently.

#### **Shipping Improvements**

The columns can be shipped pre-loaded with, for example, strontium-82. Therefore, the columns are shipped in sealed containers containing GP-100 absorbent material to absorb any leakage.

The above description is to be taken as illustrative and not in the limiting sense. Many modifications can be made to the design without deviating from the scope thereof.